Certolizumab pegol (CDP870) for rheumatoid arthritis in adults (Protocol)

Ruiz Garcia V, Burls A, Cabello López JCL, Fry- Smith AFS, Gálvez Muñoz JG, Jobanputra P, Saiz Cuenca ESC

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TABLE OF CONTENTS

[Intervention Protocol]

Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the efficacy and safety of certolizumab pegol (CDP870) and if it has clinical benefits for people with rheumatoid arthritis (RA) who do not respond well to conventional disease-modifying anti-rheumatic drugs (DMARDs).

BACKGROUND

Rheumatoid arthritis (RA) is a systemic illness whose cause is unknown, and which causes chronic inflammation of the joints. The inflammatory response can lead to progressive joint destruction, deformity and disability. Occasionally the illness can bring about complications that affect organs and systems in the body other than joints.

RA afflicts people of all ages and races equally and currently affects 0.5 to 1% of the population (Spector 1990). Population prevalence of 0.5% to 1% and a highly variable annual incidence (12-1200 per 100,000 population) depending on gender, race/ethnicity, and calendar year (Gabriel 2001).

RA commonly starts between the ages of 40 and 60 and is three times more common in women than men. Urban populations seem to be more often affected than rural populations for unknown reasons (Gabriel 2003).

The prognosis of RA is very variable: those with persistent disease may become severely disabled and life expectancy is reduced between 3 and 18 years especially in severe disease. Women have a higher mortality rate than men (Gabriel 2003).

RA has a substantial socio-economic impact. In the USA the average annual medical cost per case is $5,919 (Yelin 1999) and approximately £2,600 (McIntosh 1996) in the UK. In Spain, RA causes around 10% of total disability and 5% of transitory disability (Carmona 2002) and is commonly associated with occu-

pational disability (Doeglas 1995; Kaarela 1987).

Treatment objectives are to control symptoms of joint pain and stiffness, improve function and quality of life and minimise the risk of structural damage by reducing inflammation. These objectives may be met, and prognosis improved, by early treatment with disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, (Laird 1990; Nell 2004). Tumour necrosis factor alpha (TNF-alpha) a pro-inflammatory cytokine is a key player in the pathogenesis of RA (Scott 2006). Inhibitors of TNF-alpha, of which three are currently licensed for use in Europe and North America (adalimumab, etanercept, and infliximab), have been a major development in the treatment of RA. Randomised trials have shown that these drugs are highly effective in patients with RA who have not responded well to conventional DMARDs. TNF-alpha inhibitors have been shown to reduce the risk of joint damage (van der Heijde 2004), improve physical function (Bruce 2003) and quality of life (Chen 2006; Ware 2000). No controlled trials have compared one TNF inhibitor against another (Scott 2006). An important limitation of their wider use is their high cost, between $10,000 and $25,000 per patient per year.

Initial studies in RA with a new pegylated anti-TNF, certolizumab, (Fab fragment, pegylated anti-TNF alpha) suggest that it is well tolerated and that clinical improvement is comparable to that obtained with etanercept. The potential advantages of this drug are its long life in plasma and low manufacturing costs (Choy 2002). Pegylation of a molecule results in a longer half-life and thereby reduces the need for frequent dosing. However, lasting immunosuppression may be disadvantageous in the event of latent infections such as tuberculosis or newly acquired infections or malignancies. A systematic review of infliximab and adalimumab showed that the risk of malignancy and serious infection was increased [pooled odds ratios 3.3 (95% confidence interval [95% CI] 1.2 to 9.1) and 2.0 (95% CI 1.3 to 3.1) respectively] (Bongartz 2006).

OBJECTIVES

To determine the efficacy and safety of certolizumab pegol (CDP870) and if it has clinical benefits for people with rheumatoid arthritis (RA) who do not respond well to conventional disease-modifying anti-rheumatic drugs (DMARDs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Adults with RA who have persistent disease activity despite current or previous use of conventional disease modifying anti-rheumatic drugs (DMARDs). Patients will be identified as fulfilling the usual publishing ACR criteria for RA. Patients 18 years of age or older meeting the ACR 1987 revised criteria (Arnett 1988) for RA. Patients must have had an active form of the disease as demonstrated by at least two of the following symptoms:

1. 3 or more tender joint areas observed by a physician
2. 3 or more swollen joint areas observed by a physician
3. Duration of early morning stiffness > 30 minutes
4. Acute phase reactants such as Westergren erythrocyte sedimentation rate (ESR) more than 100 mm/ hour or C reactive Protein (CRP) more than 1 mg/mL

Types of interventions

The intervention is Certolizumab pegol (CDP870). The comparison drug may be a placebo or any disease-modifying anti-rheumatic drug including other biologic agents used to treat RA.

Types of outcome measures

Primary outcomes

The primary outcomes for this systematic review will be the percent of patients achieving an ACR 50, frequency of adverse events (serious adverse events defined according to internationally accepted criteria, malignancies, and all infections, especially tuberculosis), and Health related quality of life such HAQ and SF-36 when available. We will review also this list of adverse events: headache, fever, blood disorders, laboratory disorders, abdominal pain, nasopharyngitis, nausea, respiratory tract infections, urinary tract infections, neck pain, congestive heart failure, pruritus and anaphylaxis. All causes of discontinuations will be analysed. ACR50 is defined as a 50% improvement in the number of tender and swollen joints and a 50% improvement in at least three of the following items: observer evaluation of overall disease activity, patient evaluation of overall disease activity, patient evaluation of pain, a score of physical disability, or improvements in blood acute-phase responses.

Secondary outcomes

Secondary outcomes will be: ACR20 and ACR70 (a 20% or 70% improvement in the parameters described above); Disease Activity Score (DAS28 or other versions of DAS) and radiological changes.

Search methods for identification of studies

This task will be conducted by the information specialist Anne Fry-Smith. She will carry out the searches.
See search strategies in appendices section: MEDLINE Appendix 1; EMBASE Appendix 2; CINAHL Appendix 3; CDSR and CENTRAL, HTA, DARE, NHS EED Appendix 4; SCOPUS Appendix 5; TOXLINE (TOXNET) Appendix 6.

Electronic searches

The search strategy will be developed using a revision of the Cochrane Highly Sensitive Search Strategy (HSSS) for PubMed Glanville 2006 and the best sensitivity filter developed by the Hedges Team Wong (a) 2006; Wong (b) 2006. The strategy includes MESH headings and text terms for CDP870 and Rheumatoid Arthritis. Safety data will be obtained from clinical trials. Safety data from published cohort studies will be summarized after implementing searches for cohort studies with Rheumatoid arthritis. The search strategy will combine index and text terms for CDP870 and adverse effects reported in RCT of Certoluzimab Pegol and another anti-TNF alpha with a strategy based on Golder (a) 2006 strategy. No language restrictions will apply. Search strategies to identify studies will follow the Musculoskeletal Review Group recommendations.
A full range of databases will be reviewed including: The Cochrane Controlled Trials Register (CENTRAL), MEDLINE, EMBASE, Web of Knowledge, and Scopus. The Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) websites will also be searched. Lead researchers of identified studies will be consulted in order to obtain additional information, and also to ensure the completeness of the data sought. The time-scale for the databases consulted: CENTRAL (The Cochrane Library 2007, Issue 3); MEDLINE 1966 to October 2007; EMBASE (1980 to October 2007); HEED to October 2007. Scopus 2004 to October 2007.

Searching other resources

1. - Abstracts for the two key annual international rheumatology meetings - the American College of Rheumatology and the Congress of the European League Against Rheumatism - (2006-December 2008) will be searched.
2. - We will consult the information made available by the main researchers/sponsors and from the clinical trial meta-register database (http://www.controlled-trials.com/mrct/). When published data are missing, incomplete or inconsistent with RCT protocols, further information will be sought from the authors/manufacturers.
3. - We will review the Health Technology Assessment reports from the European, Canadian, North American and Australian national agencies.
4. - We will inspect reference lists of all identified studies for more trials.
5. - We will contact the manufacturers of Certolizumab for additional data.

Data collection and analysis

Selection of studies

Inclusion Criteria:
1. RCTs that compared Certolizumab pegol with any other agent including placebo in adult RA patients with active rheumatoid arthritis despite current or prior treatment with conventional disease modifying anti-rheumatic drugs (DMARDs).
2. Trials that are fully published as a paper or available as a complete trial report will be included. Trial reports will be requested on all major trials from the manufacturers especially where full data are unpublished.
3. We will include all studies having at least 3 months of follow-up in order to assess effectiveness. To assess safety we will also include studies having a sub-optimal length of follow-up, from 8 weeks.
Exclusion criteria:
1. Trials of Certolizumab pegol in juvenile arthritis, Crohn's disease, psoriatic arthritis and other forms of spondyloarthritis.
2. Trials of Certolizumab pegol comparing different doses or routes without another active or placebo control group, (except for use for assessing safety outcomes).
3. Studies reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms and which did not report relevant clinical outcomes.
4. Observational studies of Certolizumab pegol; interim results of trials.
Safety outcomes
Will be obtained from all RCTs that meet the inclusion criteria for the review on efficacy.

Data extraction and management

Two review authors will independently review titles and abstracts of identified studies in the search to assess studies that may potentially meet the inclusion criteria. We will resolve any disagreement by discussion, and where doubt still remains, the full article will be acquired for further inspection. Once the papers are obtained, we will decide independently if the studies meet the review criteria.
Data included in previously published peer reviews will be extracted, when possible, for intention-to-treat populations as raw numbers, plus any summary measures with standard deviations, confidence intervals and P values of outcomes reported. Any differences of opinion and data discrepancies will be resolved by involvement of a third person (Encarnación Saiz).

Through a Web interface, Vicente Ruiz & P Jobanputra will decide on which studies to include in the systematic review and will apply exclusion criteria. Here a final table will be produced in Excel format and data discrepancies will be resolved. Agreed data will be used in meta-analyses and data synthesis.

Assessment of risk of bias in included studies

Following the recommendations of Cochrane Handbook, we will use a risk of bias table to assess bias; in said table each entry addresses a specific feature of the study, the judgement for each entry involves answering a question, with answers 'Yes' indicating low risk of bias, 'No' indicating high risk of bias, and 'Unclear' indicating either lack of information or uncertainty over the potential for bias. The resulting data will be presented in a risk of bias graph (Higgins 2008).

Measures of treatment effect

Where possible, efforts will be made to convert outcome measures to dichotomous data. For dichotomous data, risk ratios will be calculated and their respective CIs (Sinclair 1994). For continuous data we will use mean differences when the results were measured in the same way in different studies. We will use standardised mean differences when the results obtained were conceptually the same but with different measurement scales. The central estimate (mean) and standard deviation will be recorded. If this is not directly stated it will be calculated from the standard error, the different means and their respective CIs or P values. When medians and interquartile ranges were the only data provided, the median will be used as a proxy measure of the mean and the difference between the first and third interquartile as equivalent to 1.35 of the SD. It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Higgins 2008). The risk difference will be used to quantify the number needed to treat (NNT) (Laupacis 1988).

Unit of analysis issues

In most of the cases the design for a clinical trial will be a simple parallel group one, in which participants are individually randomised to one of two intervention groups, and a single measurement for each outcome from each participant is collected and analysed. However, there are numerous variations on this design which we will take into account; for instance: 1) groups of individuals being randomised together to the same intervention (i.e. cluster-randomised trials); 2) individuals undergoing more than one intervention (e.g. in a cross-over trial, or simultaneous treatment of multiple sites on each individual), or 3) multiple observations for the same outcome (e.g. repeated measurements, recurring events, measurements on different body parts).

Dealing with missing data

We will carry out an intention-to-treat analysis. Everyone allocated to the intervention will count whether they completed the follow-up or not. We will assume that those who dropped out had no change in their outcome. This rule is conservative concerning response to treatment, because it assumes that those discontinuing the studies would not have responded. It is not conservative concerning adverse effects, but we felt that assuming that all those leaving early would have developed side effects would overestimate risk.

When published data is missing, incomplete or inconsistent with RCT protocols or meeting abstracts, we will ask for further information from the authors/manufacturers. We will only exclude abstracts of studies that are interim reports of studies that have not yet finished recruiting.

Assessment of heterogeneity

Heterogeneity will be explored using funnel graphics (Light 1984) and other graphics and estimators (Begg 1994; Egger 1997). We will explore heterogeneity between the trials using the chi square test for heterogeneity using a 10 % level of significance, and the I squared (I^2) test using a value of 50 % to represent moderate levels of heterogeneity.

Assessment of reporting biases

Will be explored using funnel plots and heterogeneity.

Data synthesis

The need to analyse the results according to a fixed or random effect analysis will be explored (Laird 1990) or in the event of significant heterogeneity a decision may be made to not present a combined result of the two (Schulz 1993). We will apply fixed-effect models throughout, except when heterogeneity exists, in which cases a random effects model will be used to introduce less bias than excluding trials altogether. We will pool sufficiently homogeneous studies (e.g., similarities between participants, interventions, outcome assessment, etc.). Forest plots (mean differences and risk ratios) will be produced and written and graphic information to justify the selection of certain models instead of others. Data will be analysed with Review Manager 5.

We will use "The Grades of Recommendation, Assessment, Development and Evaluation" developed by the GRADE Working Group for grading the quality of evidence. The GRADE approach specifies four levels of quality. The highest quality rating is for randomised trial evidence. Review authors can, however, downgrade randomised trial evidence to moderate, low, or even very low quality evidence, depending on the presence of five specific factors [See Handbook chapter XII (Higgins 2008)].

A program called GRADEpro will assist in the creation of Summary of Findings Tables [see Handbook chapter XII (Higgins

2008)]. Usually, quality rating will fall by one level for each factor, up to a maximum of three levels. If there are very severe problems for any one factor (e.g. when assessing limitations in design and implementation, all studies were unconcealed, unblinded, and lost over 50% of their patients to follow-up), randomised trial evidence may fall by two levels due to that factor alone.

Subgroup analysis and investigation of heterogeneity

If heterogeneity were detected then a sub-group analysis would be carried out (Yusuf 1991), and/or a meta-regression in order to explain it (Thompson 1999). Subgroup analyses are planned for the duration of the illness (approximately 3 years evolution, patients' sex, dose, administration and methodological quality).

Sensitivity analysis

We will perform sensitivity analyses by assessing different treatment combinations, timing of drug initiation, trial design (adequate allocation concealment, blinding of patients and outcome assessors, and withdrawals and dropouts less than 15%.Trial results will be entered into RevMan 5 using the same plot direction to enable the pooling of results where the lowest value has improved and the highest value has worsened. Negative values in SMD will indicate a benefit of the active drug over the placebo.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

Search strategy for effectiveness:
1. (CDP870 or CDP 870 or "certolizumab pegol" or certolizumab or CDP-870 or cimzia).mp.
2. . ("Rheumatoid Arthritis" or (Caplan$ and Syndrome?) or (Felty$ and S?ndrome) or (Rheumatoid and Nodule?) or (Sjogren$ and S?ndrome?) or (Sicca$ and S?ndrome?) or (Ankylos$ and Spondylit$) or (Spondylarthritis and Ankylopoietica) or (Rheumatoid$ and Spondylit$) or (Bechterew$ and Disease?) or (Marie-Struempell and Disease?) or (Adult and Onset and Still$ and Disease?)).mp.
3.. exp Arthritis, Rheumatoid/
4. (2 OR 3)
5. 1 AND 4
6. Clinical trial.pt.
7. randomized.ab.
8. Placebo.ab.
9. dt.fs.
10. randomly.ab.
11. trial.ab.
12. groups.ab.
13. or/ 6-12
14. 5 and 13
Search strategy for Safety:
#1. Exp Headache/ci OR Exp Nasopharyngitis/ci OR Exp Arthritis, Rheumatoid/ci OR Exp Nausea/ci OR Exp Infection/ci OR Exp Respiratory Tract Infections/ci OR Exp Urinary Tract Infections/ci OR Exp Neck Pain/ci OR Exp Antibodies, Antinuclear/ci OR Exp Granulomatous Disease, Chronic/ci OR Exp Granulomatous Disease, Chronic/ci OR Exp Tuberculosis/ci OR Exp Histoplasmosis/ci OR Exp Neoplasms/ci OR Exp Skin Neoplasms/ci OR Exp Hematologic Neoplasms/ci OR Exp Death/ci OR Exp Sepsis/ci OR Exp Abdominal Pain/ci OR Exp Heart Failure, Congestive/ci OR Exp Fever/ci OR Exp Pruritus/ci OR Exp Melanoma/ci OR Exp Lymphoma/ci OR Exp Pneumonia/ci OR Exp Lupus/ci OR Exp Lupus Erythematosus, Systemic/ci OR Exp Anaphylaxis/ci OR "blood disorders".ab,ti. OR "laboratory test abnormalities".ab,ti. OR Headache.ab,ti. OR Nasopharyngitis.ab,ti. OR "Rheumatoid Arthritis".ab,ti. OR Nausea.ab,ti. OR Infection.ab,ti. OR "Respiratory Tract Infections".ab,ti. OR "Urinary Tract Infections" .ab,ti. OR "Neck Pain".ab,ti. OR "Antinuclear Antibodies".ab,ti. OR "Chronic Granulomatous Disease" .ab,ti. OR Tuberculosis.ab,ti. OR Histoplasmosis.ab,ti. OR Neoplasms.ab,ti. OR "Skin Neoplasms".ab,ti. OR "Hematologic Neoplasms".ab,ti. OR Death.ab,ti. OR Sepsis.ab,ti. OR "Abdominal Pain" .ab,ti. OR "Heart Failure".ab,ti. OR Fever.ab,ti. OR Pruritus.ab,ti. OR Melanoma.ab,ti. OR Lymphoma.ab,ti. OR Pneumonia.ab,ti. OR Lupus.ab,ti. OR "Lupus Erythematosus".ab,ti. OR Anaphylaxis.ab,ti.
#2. ae.fs OR po.fs OR to.fs OR de.fs OR co.fs
#3. (advers$.ab,ti. OR untoward$.ab,ti. OR avers$.ab,ti. OR detrimental$.ab,ti. OR damage$.ab,ti. OR harmful$.ab,ti. OR cripple$.ab,ti. OR prejudicial$.ab,ti. OR disruptiv$.ab,ti. OR destructive$.ab,ti. OR deleter$.ab,ti. OR untoward$.ab,ti. OR unexpect$.ab,ti. OR side$.ab,ti. OR serious$.ab,ti. OR severe$.ab,ti. OR unlikely$.ab,ti. OR malignan$.ab,ti.) AND (consequenc$.ab,ti. OR implication$.ab,ti. OR result$.ab,ti. OR outgrowth$.ab,ti. OR repercussion$.ab,ti. OR episod$ .ab,ti. OR happen$.ab,ti. OR reaction$.ab,ti. OR effect$.ab,ti. OR experience$.ab,ti.) OR complication$.tw.
#4. Exp Drug Toxicity
#5. 1 OR 2 OR 3 OR 4
#6. CDP870 OR CDP870 or CDP 870 or "certolizumab pegol" or certolizumab or CDP-870 or cimzia.mp.
#8. 5 AND 6

Appendix 2. EMBASE search strategy

Search strategy for effectiveness:
1. 'rheumatoid arthritis'/exp/
2. 'certolizumab pegol'/exp/
3. (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
4. 2 OR 3
5. 4 AND 1
6. random:.tw.
7. clinical trial:.mp.
8. exp health care quality
9. or/6-8
10. 5 AND 9
Search strategy for safety:
#1 exp Headache/si or exp Nasopharyngitis/si or exp Arthritis, Rheumatoid/si or exp Nausea/si or exp Infection/si or exp Respiratory Tract Infections/si or exp Urinary Tract Infections/si or exp Neck Pain/si or exp Antibodies, Antinuclear/si or exp Granulomatous Disease, Chronic/si or exp Granulomatous Disease, Chronic/si or exp Tuberculosis/si or exp Histoplasmosis/si or exp Neoplasms/si or exp Skin Neoplasms/si or exp Hematologic Neoplasms/si or exp Death/si or exp Sepsis/si or exp Abdominal Pain/si or exp Heart Failure, Congestive/si or exp Fever/si or exp Pruritus/si or exp Melanoma/si or exp Lymphoma/si or exp Pneumonia/si or exp Lupus/si or exp Lupus Erythematosus, Systemic/si or exp Anaphylaxis/si or "blood disorders".ab,ti. or "laboratory test abnormalities".ab,ti. or Headache.ab,ti. or Nasopharyngitis.ab,ti. or "Rheumatoid Arthritis".ab,ti. or Nausea.ab,ti. or Infection.ab,ti. or "Respiratory Tract Infections".ab,ti. or "Urinary Tract Infections".ab,ti. or "Neck Pain".ab,ti. or "Antinuclear Antibodies".ab,ti. or "Chronic Granulomatous Disease".ab,ti. or Tuberculosis.ab,ti. or Histoplasmosis.ab,ti. or Neoplasms.ab,ti. or "Skin Neoplasms".ab,ti. or "Hematologic Neoplasms".ab,ti. or Death.ab,ti. or Sepsis.ab,ti. or "Abdominal Pain".ab,ti. or "Heart Failure".ab,ti. or Fever.ab,ti. or Pruritus.ab,ti. or Melanoma.ab,ti. or Lymphoma.ab,ti. or Pneumonia.ab,ti. or Lupus.ab,ti. or "Lupus Erythematosus".ab,ti. or Anaphylaxis.ab,ti.
#2 (ae or to or co).fs.
#3 (((advers$ or untoward$ or avers$ or detrimental$ or damage$ or harmful$ or cripple$ or prejudicial$ or disruptiv$ or destructive$ or deleter$ or untoward$ or unexpect$ or side$ or serious$ or severe$ or unlikely$ or malignan$) and (consequenc$ or implication$ or result$ or outgrowth$ or repercussion$ or episod$ or happen$ or reaction$ or effect$ or experience$)) or complication$).tw.
#4 exp Adverse drug reaction/ or exp Side-effect/ or exp Drug Toxicity
#5 or/1-4
#6 CDP870.rn OR (CDP870 or CDP 870 or "certolizumab pegol" or certolizumab or CDP-870 or cimzia).mp.
#7 5 AND 6

Appendix 3. CINAHL search strategy

Search strategy for effectiveness:
1.'rheumatoid arthritis'/exp/
2."rheumatoid arthritis".mp.
3. (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
4.(1 or 2) and 3
5.exp prognosis
6.exp study design
7.random:.mp.
8.or/ 5-7
9.4 and 8

Appendix 4. Search strategy for CDSR and CENTRAL, HTA, DARE, NHS EED

Search strategy for effectiveness:
Cochrane Database of Systematic Reviews, Health Technology Assessment (HTA), The Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) from Ovid:
1.'rheumatoid arthritis'.mp.
2.(CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
3.1 and 2
Search strategy for safety:
DARE, CDSR and CENTRAL from OVID platform (version 10.5.1), will be searched up to October 2007, The search strategy will combine text and index terms for CDP870 and adverse effects reported in RCTs of Certoluzimab Pegol and another anti-TNF alpha with a strategy based on that by Golder (b) 2006.
#1 Drug and (hypersensitive$ or tocit$).tw.
#2 ((safe$ or advers$ or tolerabilit$ or toxic$ or adr$ or tolera$ or harm$ or complicat$ or risk$) adj20 objective$).tw.
#3 (side adj3 effect$ adj20 objective$).tw.
#4 (undesirable adj3 effect$ adj20 objetive$).tw.
#5 (treatment adj3 emergent adj20 objective$).tw.
#6 or/1-5
#7 (CDP870 or CDP 870 or certolizumab pegol or certolizumab or CDP-870 or cimzia).tw.
#8 6 and 7

Appendix 5. SCOPUS search strategy

Search strategy for effectiveness:
SCOPUS will be searched up to August of 2007, without limits of years:
KEY((certolizumab OR cimzia OR CDP-870 OR CDP870 OR "CDP 870") AND ("rheumatoid arthritis"))
Web of Knowledge (WOK), was searched up to August of 2007, without limits of years. The search strategy is as follows:
topic=((certolizumab OR cimzia OR CDP-870 OR CDP870 OR "CDP 870") AND ("rheumatoid arthritis")
Databases=MEDLINE, Current Contents Connect, Web of Science, Derwent Innovations Index, ISI Proceedings; Timespan=All Years

Appendix 6. TOXLINE (TOXNET) search strategy

Search strategy for safety:
TOXLINE (TOXNET) will be searched up to October 2007. The search strategy will combine index and text terms for CDP870:
#1. certolizumab OR "certolizumab pegol" OR CDP870 OR CDP-870 OR "CDP 870" OR cimzia

WHAT'S NEW

Date	Event	Description
3 April 2008	Amended	CMSG ID: C001-P

HISTORY

Protocol first published: Issue 1, 2009

CONTRIBUTIONS OF AUTHORS

Design the protocol: Juan Cabello & Vicente Ruiz & Amanda Burls

Write up the background: Saiz E; Gosalvez J; P Jobanputra

Develop the search strategy: Anne Fry Smith

Trial search (2 people): Vicente Ruiz & P Jobanputra

Obtain copies of the trials: Anne Fry Smith

Selection of trials for inclusion (2 + 1) : Vicente Ruiz & P Jobanputra. If data-discrepancies will be resolved by involvement of a third person: Saiz E

Retrieval of trial data on effectiveness (two people): Vicente Ruiz & P Jobanputra. If data-discrepancies will be resolved by involvement of a third person: Saiz E

Data input in Revman: STATA: Vicente Ruiz

Carry out analyses: Vicente Ruiz & P Jobanputra

Interpret analyses: Juan Cabello & Amanda Burls

Write up results: Juan Cabello & Vicente Ruiz & Amanda Burls, Gosalvez J & P Jobanputra

Update effectiveness review: Vicente Ruiz & Juan Cabello & Amanda Burls& Gosalvez J

DECLARATIONS OF INTEREST

Dr Paresh Jobanputra has previously been involved in industry sponsored clinical trials of the TNF inhibitors adalimumab and etanercept. He has also received funding for educational purposes from Wyeth and Abbott Laboratories manufacturers of these drugs.

Dr. Jose Galvez and Dr. Encarnación Saez have, in the past, been involved in two randomised clinical trials, one phase III with etoricoxib sponsored by MSD and a phase IV study with etanercept sponsored by Wyeth.

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Internal sources

- CI+DEC, Spain.

External sources

- No sources of support supplied